**Name of journal: World Journal of Gastroenterology**

**ESPS Manuscript NO: 6815**

**Columns:** **REVIEW**

**MicroRNAs: New therapeutic targets for intestinal barrier dysfunction**

Zhang L *et al.* MicroRNA in intestinal barrier dysfunction treatment

Lin Zhang, Jian Cheng, Xiao-Ming Fan

**Lin Zhang, Jian Cheng, Xiao-Ming Fan,** Department of Gastroenterology and Hepatology, Jinshan Hospital of Fudan University, Shanghai 201508, China

**Author contributions:** Fan XM conceived the topic and revised the paper; Zhang L reviewed the literature and wrote the paper; Cheng J reviewed the literature.

**Supported by** Grant for key clinical discipline construction of Shanghai Municipality, China, No. ZK2012B20 and phase II outstanding young medical personnel training fund of Jinshan District Health Systems, Shanghai, China, No. JWKJ-RCYQ-201207

**Correspondence to:** **Xiao-Ming Fan, MD, PhD,** Department of Gastroenterology and Hepatology, Jinshan Hospital of Fudan University, No. 1508, Longhang Road, Shanghai 201508, China. xiaomingfan57@sina.com

**Telephone:** +86-21-34189990-5389 **Fax:** +86-21-57943141

**Received:** October 28, 2013 **Revised:** December 9, 2013

**Accepted:** January 14, 2014

**Published online:**

**Abstract**

Defects in intestinal barrier function characterized by an increase in intestinal permeability contribute to intestinal inflammation. Growing evidence has shown that an increase in intestinal permeability has a pathogenic role in diseases such as inflammatory bowel disease (IBD) and celiac disease, and functional bowel disorders such as irritable bowel syndrome. Therefore, clarification of the inflammatory responses, the defense pathway and the corresponding regulatory system is essential and may lead to the development of new therapies. MicroRNAs (miRNAs) are small (19-22 nt) noncoding RNA molecules that regulate genes at the post-transcriptional level by base-pairing to specific messenger RNAs for degradation to repress translation. Recent studies suggested that miRNAs are important in the immune response and mediate a critical role in multiple immune response-related disorders. Based on these discoveries, attention has been focused on understanding the role of miRNAs in regulating intestinal barrier dysfunction, especially in IBD. Here, we provide a review of the most recent state-of-the-art research on miRNAs in intestinal barrier dysfunction.

© 2014 Baishideng Publishing Group Co., Limited. All rights reserved.

**Key words:** MicroRNAs; Intestinal barrier dysfunction; Inflammatory bowel disease; Celiac disease; Therapeutic target

**Core tip:** This article summarizes the latest findings on the important roles of microRNAs (miRNAs) in regulating inflammation and autoimmune disorders in inflammatory bowel disease (IBD). Insight into miRNAs-21 as a novel biomarker is also provided which shows that miRNAs-21 is a potential diagnostic and therapeutic target for IBD.

Zhang L, Cheng J, Fan XM.MicroRNAs: New therapeutic targets for intestinal barrier dysfunction.

*World J Gastroenterol* 2013;

**Available from:**

**DOI:**

**INTRODUCTION**

The intestinal barrier plays an important role in absorbing nutrients and secreting waste[1]. In addition to its abilities to support paracellular transport, the intestinal barrier can also prevent luminal microbes and their products reaching the internal milieu. Tight junctions and their associated proteins, including claudins, occludin, and zonula occludens are the most adhesive apical junctional complexes and act as a structural and functional barrier against paracellular permeation of luminal substances[2-4]. Breakdown or disruption of the epithelial barrier is thought to be an essential determinant in the predisposition to intestinal inflammation and a number of inflammatory disorders, such as Crohn’s disease[5], ulcerative colitis[6,7], celiac disease[8], and a series of infectious diarrheal syndromes[9,10]. The phenomenon of intestinal tight junction (TJ) barrier disruption has previously been reported, but the intracellular mechanism is still poorly understood. Of the essential factors relating to this issue, two are most critical. The first is to identify the early signaling event which triggers the immune response and inflammatory cascade which will help us to understand induction of the disease, and the second is to identify the regulatory system which will lead to the discovery of the therapeutic target. MicroRNAs (miRNAs), which are small noncoding RNAs, were recently discovered to have a promising role in the treatment of immune-related diseases[11,12]. By regulating the degradation of mRNAs at the post-transcriptional level, miRNAs can also affect the signaling pathway, and may be good candidates for the treatment of immune-related diseases. More recently, investigations have focused on the role of miRNAs in intestinal-related diseases. These studies may not only provide novel insights into understanding the pathological and physiological process of intestinal barrier dysfunction, especially in IBD, but have also suggested the therapeutic role played by miRNAs. The major purpose of this review was to examine current research on the role of miRNAs in the regulation of intestinal barrier function and their therapeutic potential.

**MIRNAS BIOGENESIS AND FUNCTION**

MiRNAs, non-coding small endogenous RNAs of 19-22 nucleotides in length, were first identified in [*C.* *HYPERLINK "http://en.wikipedia.org/wiki/Caenorhabditis\_elegans"elegans*](http://en.wikipedia.org/wiki/Caenorhabditis_elegans) by Lee *et al*[13] in a study on the function of gene *lin-14* as a sequence-specific regulator of gene expression[14]. MiRNAs which are encoded by eukaryotic nuclear DNA can target the 3' untranslated region (3'UTR) of specific mRNAs, usually resulting in gene downregulation *via* translational repression or target degradation[15]. More than 1500 miRNAs have been found to be encoded in the human genome and over 60% of human genes are targeted by miRNAs[16-18]. miRNAs play an important role in many different types of human cells[19].

RNA polymerase II (*Pol II*) is associated with the miRNA promoter and induces primary miRNAs (pre-miRNAs) to be transcribed in the nucleus[20,21]. These pre-miRNAs have a capped structure and a poly(A) tail[20,22]. After being transported to the cytoplasm, the pre-miRNAs are further processed by the RNase III endonuclease, Dicer, in a complex with a trans-activator RNA binding protein into a double-stranded mature miRNA[23-25]. One strand of the mature miRNA is then incorporated into the RNA-induced silencing complex (RISC) and leads this complex to the untranslated region (3'UTR) of specific mRNAs, which causes repression of the corresponding protein[26-29]. In this way, miRNAs are thought to be fine-tune regulators in gene expression and disease control.

A number of biological processes are regulated by miRNAs, such as cell proliferation, apoptosis, differentiation, migration and cell cycle control[30-33]. miRNAs have also been reported to be involved in human diseases, including tumor[34-41], immune dysregulation[42-44], cardiovascular disease[45-48], metabolic syndrome[49,50] and others[51].

**EXPRESSION OF MIRNAS IN INTESTINAL EPITHELIAL CELLS**

In 2008, Wu *et al*[52] first reported miR-192 which was detected in the epithelial cells of colonic mucosa samples from healthy individuals, but not in patients with active UC using immunohistochemistry and *in situ* hybridization. These authors also found 11 differentially expressed miRNAs in active UC *vs* healthy samples and confirmed an inverse relationship between macrophage inflammatory peptide-2α (*MIP-2α*, previously shown to be involved in IBD[53]) and miR-192. Similarly, Bian *et al*[54] demonstrated that miR-150 was significantly increased in the epithelial cells of colonic mucosa in UC patients compared with controls, and suggested an inverse correlation between miR-150 and its target, *c-Myb*[55], a proto-oncogene involved in apoptosis. Consequently, these two pioneer studies have provided new insight into the pathogenesis of intestinal barrier dysfunction. A summary of the expression of miRNAs in IBD is shown in.

**ROLE OF MIRNAS IN TIGHT JUNCTION PROTEINS**

Occludin and claudins are important transmembrane TJ proteins localized at the TJ strands and function in the TJ barrier[56-58]. Ye *et al*[59] demonstrated that miR-122a plays a central role in the regulation of intestinal TJ permeability by degrading the protein occludin. The regulation of claudins by miRNAs was reported in breast cancer[60,61] and HIV-associated neurological disorders[62], but not in the intestinal TJ barrier. Further studies on the relationship between claudins and miRNAs in the intestinal TJ barrier system are required. Zonula occludens 1 (*ZO-1*) is another major component of the TJ barrier which regulates intestinal permeability[63]. Tang *et al*[64] found miR-212 overexpression in colon biopsy samples from patients with alcoholic liver disease and in Caco-2 cells (a human intestinal epithelial cell line) treated with ethanol. Alcohol can induce miR-212 overexpression and leads to gut leakiness by down-regulating *ZO-1* translation.

**MIRNAS AND INFLAMMATION**

Many groups have demonstrated that miRNAs play pivotal roles in both adaptive and innate immunity[65]. miRNAs regulate the development of various immune cells as well as their immunological functions. miRNAs are also essential in B- and T-cell function. A deficiency in Dicer, the key enzyme in processing miRNAs, results in inhibition of T cell development[65]. In addition, several miRNAs, including miR-155, miR-181a, miR-150 and the miR-17-92 cluster, are also involved in B- and T-cell regulation[66]. Forced overexpression of miR-150 blocks B cell development[67]. Innate immune responses provide the initial defense against pathogens. Pattern recognition receptors, such as Toll-like receptor (TLR), expressed on macrophages and dendritic cells (DC), are regulated by miRNAs. miRNAs have also been shown to be important in regulation of the TLR signaling cascade[68,69]. MiR-146a expression can be induced by exposure to TLR ligands, such as lipopolysaccharide (LPS), peptidoglycan, and flagellin[70]. miR-146a then functions in a negative feedback mechanism in the TLR signaling cascade by decreasing the expression of TNF-receptor-associated factor(*TRAF*)-*6* and IL-1 receptor associated kinase (*IRAK*)*-1*, two target genes of the TLR signaling cascade. Furthermore, loss of miR-155 in DC impairs its antigen presenting capacity and costimulation activity. The target gene of miR-155 in DC is *SOCS1* which negatively regulates antigen presenting capacity in DC. Therefore, deregulation of *SOCS1* in the absence of miR-155 could account for impaired DC function[71]. In macrophages, the downregulation of miR-125b is required to ensure that the correct inflammatory response is produced[72]. The idea of miRNAs as regulators of IBD provides new insight into the development of appropriate therapies.

**MIRNAS AND AUTOIMMUNE RESPONSE IN IBD**

Several studies have reported that miRNAs are involved in autoimmune diseases (AID)[42-44]. As miRNAs have been confirmed to play a role in immune cell development and have an impact on cell functions, it is reasonable to deduce that miRNAs are related to AID. Reports have shown that miRNAs take part in AID, such as rheumatoid arthritis[73], systemic lupus erythematosus[74], multiple sclerosis[75], primary biliary cirrhosis[76], inflammatory bowel disease[52], idiopathic thrombocytopenic purpura[77] and psoriasis[78].

Inflammatory bowel disease (IBD), including Crohn's disease (CD) and ulcerative colitis (UC), is a chronic gastrointestinal inflammatory disorder in which the pathophysiology has been extensively studied over the past several years, but is still poorly understood.

Wu and colleagues[52] studied mucosal tissue from healthy subjects and UC patients and found that miR-192 was predominantly expressed in the intestinal epithelial tissue of healthy subjects and was significantly decreased in UC patients. Furthermore, they also observed that the inflammatory protein, *MIP-2,* was mainly expressed in UC patients and was decreased in healthy subjects. The expression of *MIP-2α* had an inverse relationship with miR-192. Besides miR-192, they also identified several other differentially expressed miRNAs between UC patients and healthy subjects. MiR-21 was increased in UC patients compared with healthy subjects. miR-375, miR-422b and miR-23a were increased in healthy subjects and all three miRNAs had a similar level of expression in inactive UC[52]. A previous study also showed that *TGF-β* can induce miR-192[79]. This suggests that miR-192 may be the master regulator in the process of inflammation. These findings indicate that miRNAs are involved in the pathogenesis of IBD.

**MIRNAS AND MITOCHONRIAL STRESS IN IBD**

Mitochondria are fundamental subcellular components that play a critical role in the maintenance of normal structure, function and survival of cells. Mitochondrial dysfunction is associated with metabolic diseases including insulin resistance, obesity, diabetes, and the cardiorenal metabolic syndrome[80-83]. Growing evidence suggests that miRNAs provide another layer of regulation with regard to mitochondrial function. MiR-338 can modulate mitochondrial function by targeting cytochorome c oxidase IV(*COX IV*) mRNA[84]. The miRNA-200 family is implicated in epithelial-to-mesenchymal transition (EMT) which is accompanied by mitochondrial biogenesis and is involved in organ fibrosis and carcinoma progression[85]. Nishi *et al*[86] showed that miR-15b, miR-195 and miR-424 can down-regulate cellular ATP levels and affect mitochondrial integrity. In addition, miR-23a/b in hypertrophy acts in a compensatory mechanism to down-regulate mitochondrial glutaminase (GLS)[87]. More recently, Yuan *et al*[88] suggested that Prohibitin which can inhibit mitochondrial dysfunction may be a potential target in IBD. However, further studies are required to determine whether miRNAs can affect IBD by regulating mitochondrial function.

**MIRNAS AND AUTOPHAGY IN IBD**

Autophagy is a unique cellular process of self-digestion, characterized by the engulfment of cytosolic macromolecules and organelles in a autophagosome which are then transported to the lysosome for degradation[89,90]. Autophagy helps to recycle and store nutrients for stress conditions[89].

Recently, autophagy-related gene(*ATG*) *16L1* was reported to be involved in CD[91,92]. *ATG 16L1* shares some sequence homology with yeast *Apg16L* and was originally identified in the protein complex *ATG5*-*ATG12*[93]. In autophagy, *ATG16L* plays an important role in autophagosome formation and functions as an E3-like enzyme to mediate lipidation[94]. Lu *et al*[95]recently provided evidence to show that miR106b and miR93 suppress autophagy-mediated removal of bacteria in epithelial cells by targeting *ATG16L1*. Furthermore, *NOD2*, an intracellular bacterial sensor of the nucleotide-binding and oligomerization domain (NOD)-like receptor (*NLR*) family, can sense the presence of muramyl dipeptide (MDP), a component of the peptidoglycan cell wall from both Gram-positive and Gram-negative bacteria. *NOD2* activation results in pro-inflammatory and anti-bacterial molecule production dependent on cell signaling pathways mediated by *RICK*/*RIP2*, *NF-κB* and *MAPKs*. More recently, Ghorpade *et al*[96]found that miR-146a-mediated *NOD2*-*SHH* signaling regulated gut inflammation in a mouse model of IBD.In addition, Brest *et al*[97]demonstrated that the miR-196 family of miRNAs downregulates the CD protective variant (*c.313C*) of the immunity-related GTPase family M protein 1(*IRGM1*) gene in CD patients. Consequently, the control of intracellular replication of CD-associated adherent invasive *E. coli* (AIEC) by autophagy was lost due to a decrease in *IRGM1*[97]. By targeting the related gene, miRNAs may eventually contribute to the improvement of IBD.

**NOVEL BIOMARKERES AND THERAPEUTIC TARGETS IN IBD**

With regard to the involvement of miRNAs in the pathogenesis of IBD, it is vital to identify which miRNAs are consistently dysregulated in IBD and the target genes of the miRNAs. miR-21, the most investigated and well-described miRNA, also known as the “oncomiR”, has been shown to have potential clinical application[98]. According to published data[52,53,99,100], miR-21 is the only miRNA usually upregulated in inflamed tissue or serum in IBD patients. The expression of miR-21 is regulated by *NF-κB* which is a master gene in multiple immune diseases (including IBD)[101]. Thus, miR-21 has the potential as a biomarker. Iborra *et al*[102] recently conducted a study to establish the specific expression patterns of miRNAs in the serum and mucosa of IBD patients. They identified six and five differentially expressed miRNAs in the serum and mucosa of active CD compared with inactive CD patients, respectively. Their study again suggested the utility of miRNAs as possible biomarkers. The actual role of miRNAs in IBD still need to be confirmed by functional studies, however, miRNAs have shown promise in the treatment of IBD.

**CONCLUSION**

Recently, increasing attention has been paid to the gene expression of miRNAs in IBD. Clinical trials have been carried out to test the therapeutic efficacy of miRNA-based therapies. “Miravirsen”, a specific inhibitor of miR-122, is now being evaluated in a phase II clinical trial[103]. Furthermore, a recent review[104] suggested the use of an miRNA inhibitor or synthetic miRNA targeting the *PI3K* and *Ras/MAPK* pathways in multiple myeloma (MM) treatment. MiR-29b is a promising target in MM treatment by multiple mechanisms, including the regulation of osteoclastic differentiation[105] and epigenetic regulation of the cell cycle[106, 107]. Future studies will provide a basis for more clinical trials and shed light on miRNA-based therapies in IBD.

**REFERENCES**

1 **Shen L**, Su L, Turner JR. Mechanisms and functional implications of intestinal barrier defects. *Dig Dis* 2009; **27**: 443-449 [PMID: 19897958 DOI: 10.1159/000233282]

2 **Groschwitz KR**, Hogan SP. Intestinal barrier function: molecular regulation and disease pathogenesis. *J Allergy Clin Immunol* 2009; **124**: 3-20; quiz 21-2 [PMID: 19560575 DOI: 10.1016/j.jaci.2009.05.038]

3 **Groschwitz KR**, Ahrens R, Osterfeld H, Gurish MF, Han X, Abrink M, Finkelman FD, Pejler G, Hogan SP. Mast cells regulate homeostatic intestinal epithelial migration and barrier function by a chymase/Mcpt4-dependent mechanism. *Proc Natl Acad Sci U S A* 2009; **106**: 22381-22386 [PMID: 20018751 DOI: 10.1073/pnas.0906372106]

4 **Ulluwishewa D**, Anderson RC, McNabb WC, Moughan PJ, Wells JM, Roy NC. Regulation of tight junction permeability by intestinal bacteria and dietary components. *J Nutr* 2011; **141**: 769-776 [PMID: 21430248 DOI: 10.3945/jn.110.135657]

5 **Sartor RB**. Mechanisms of disease: pathogenesis of Crohn's disease and ulcerative colitis. *Nat Clin Pract Gastroenterol Hepatol* 2006; **3**: 390-407 [PMID: 16819502 DOI: 10.1038/ncpgasthep0528]

6 **Clavel T**, Haller D. Bacteria- and host-derived mechanisms to control intestinal epithelial cell homeostasis: implications for chronic inflammation. *Inflamm Bowel Dis* 2007; **13**: 1153-1164 [PMID: 17476679 DOI: 10.1002/ibd.20174]

7 **Werner T**, Haller D. Intestinal epithelial cell signalling and chronic inflammation: From the proteome to specific molecular mechanisms. *Mutat Res* 2007; **622**: 42-57 [PMID: 17628614 DOI: 10.1016/j.mrfmmm.2007.05.010]

8 **Brandtzaeg P**. Update on mucosal immunoglobulin A in gastrointestinal disease. *Curr Opin Gastroenterol* 2010; **26**: 554-563 [PMID: 20693891 DOI: 10.1097/MOG.0b013e32833dccf8]

9 **Gecse K**, Róka R, Ferrier L, Leveque M, Eutamene H, Cartier C, Ait-Belgnaoui A, Rosztóczy A, Izbéki F, Fioramonti J, Wittmann T, Bueno L. Increased faecal serine protease activity in diarrhoeic IBS patients: a colonic lumenal factor impairing colonic permeability and sensitivity. *Gut* 2008; **57**: 591-599 [PMID: 18194983 DOI: 10.1136/gut.2007.140210]

10 **Gadewar S**, Fasano A. Current concepts in the evaluation, diagnosis and management of acute infectious diarrhea. *Curr Opin Pharmacol* 2005; **5**: 559-565 [PMID: 16207535 DOI: 10.1016/j.coph.2005.08.002]

11 **Kloosterman WP**, Plasterk RH. The diverse functions of microRNAs in animal development and disease. *Dev Cell* 2006; **11**: 441-450 [PMID: 17011485 DOI: 10.1016/j.devcel.2006.09.009]

12 **Esteller M**. Non-coding RNAs in human disease. *Nat Rev Genet* 2011; **12**: 861-874 [PMID: 22094949 DOI: 10.1038/nrg3074]

13 **Lee RC**, Feinbaum RL, Ambros V. The C. elegans heterochronic gene lin-4 encodes small RNAs with antisense complementarity to lin-14. *Cell* 1993; **75**: 843-854 [PMID: 8252621]

14 **Chen K**, Rajewsky N. The evolution of gene regulation by transcription factors and microRNAs. *Nat Rev Genet* 2007; **8**: 93-103 [PMID: 17230196 DOI: 10.1038/nrg1990]

15 **Bartel DP**. MicroRNAs: target recognition and regulatory functions. *Cell* 2009; **136**: 215-233 [PMID: 19167326 DOI: 10.1016/j.cell.2009.01.002]

16 **Bentwich I**, Avniel A, Karov Y, Aharonov R, Gilad S, Barad O, Barzilai A, Einat P, Einav U, Meiri E, Sharon E, Spector Y, Bentwich Z. Identification of hundreds of conserved and nonconserved human microRNAs. *Nat Genet* 2005; **37**: 766-770 [PMID: 15965474 DOI: 10.1038/ng1590]

17 **Lewis BP**, Burge CB, Bartel DP. Conserved seed pairing, often flanked by adenosines, indicates that thousands of human genes are microRNA targets. *Cell* 2005; **120**: 15-20 [PMID: 15652477 DOI: 10.1016/j.cell.2004.12.035]

18 **Friedman RC**, Farh KK, Burge CB, Bartel DP. Most mammalian mRNAs are conserved targets of microRNAs. *Genome Res* 2009; **19**: 92-105 [PMID: 18955434 DOI: 10.1101/gr.082701.108]

19 **Lim LP**, Lau NC, Weinstein EG, Abdelhakim A, Yekta S, Rhoades MW, Burge CB, Bartel DP. The microRNAs of Caenorhabditis elegans. *Genes Dev* 2003; **17**: 991-1008 [PMID: 12672692 DOI: 10.1101/gad.1074403]

20 **Lee Y**, Kim M, Han J, Yeom KH, Lee S, Baek SH, Kim VN. MicroRNA genes are transcribed by RNA polymerase II. *EMBO J* 2004; **23**: 4051-4060 [PMID: 15372072 DOI: 10.1038/sj.emboj.7600385]

21 **Zhou X**, Ruan J, Wang G, Zhang W. Characterization and identification of microRNA core promoters in four model species. *PLoS Comput Biol* 2007; **3**: e37 [PMID: 17352530 DOI: 10.1371/journal.pcbi.0030037]

22 **Cai X**, Hagedorn CH, Cullen BR. Human microRNAs are processed from capped, polyadenylated transcripts that can also function as mRNAs. *RNA* 2004; **10**: 1957-1966 [PMID: 15525708 DOI: 10.1261/rna.7135204]

23 **Lund E**, Güttinger S, Calado A, Dahlberg JE, Kutay U. Nuclear export of microRNA precursors. *Science* 2004; **303**: 95-98 [PMID: 14631048 DOI: 10.1126/science.1090599]

24 **Okada C**, Yamashita E, Lee SJ, Shibata S, Katahira J, Nakagawa A, Yoneda Y, Tsukihara T. A high-resolution structure of the pre-microRNA nuclear export machinery. *Science* 2009; **326**: 1275-1279 [PMID: 19965479 DOI: 10.1126/science.1178705]

25 **Lee Y**, Ahn C, Han J, Choi H, Kim J, Yim J, Lee J, Provost P, Rådmark O, Kim S, Kim VN. The nuclear RNase III Drosha initiates microRNA processing. *Nature* 2003; **425**: 415-419 [PMID: 14508493 DOI: 10.1038/nature01957]

26 **Gregory RI**, Chendrimada TP, Cooch N, Shiekhattar R. Human RISC couples microRNA biogenesis and posttranscriptional gene silencing. *Cell* 2005; **123**: 631-640 [PMID: 16271387 DOI: 10.1016/j.cell.2005.10.022]

27 **Selbach M**, Schwanhäusser B, Thierfelder N, Fang Z, Khanin R, Rajewsky N. Widespread changes in protein synthesis induced by microRNAs. *Nature* 2008; **455**: 58-63 [PMID: 18668040 DOI: 10.1038/nature07228]

28 **Lim LP**, Lau NC, Garrett-Engele P, Grimson A, Schelter JM, Castle J, Bartel DP, Linsley PS, Johnson JM. Microarray analysis shows that some microRNAs downregulate large numbers of target mRNAs. *Nature* 2005; **433**: 769-773 [PMID: 15685193 DOI: 10.1038/nature03315]

29 **Bartel DP**. MicroRNAs: genomics, biogenesis, mechanism, and function. *Cell* 2004; **116**: 281-297 [PMID: 14744438]

30 **McKenna LB**, Schug J, Vourekas A, McKenna JB, Bramswig NC, Friedman JR, Kaestner KH. MicroRNAs control intestinal epithelial differentiation, architecture, and barrier function. *Gastroenterology* 2010; **139**: 1654-164, 1664.e1 [PMID: 20659473 DOI: 10.1053/j.gastro.2010.07.040]

31 **Miska EA**. How microRNAs control cell division, differentiation and death. *Curr Opin Genet Dev* 2005; **15**: 563-568 [PMID: 16099643 DOI: 10.1016/j.gde.2005.08.005]

32 **Schickel R**, Boyerinas B, Park SM, Peter ME. MicroRNAs: key players in the immune system, differentiation, tumorigenesis and cell death. *Oncogene* 2008; **27**: 5959-5974 [PMID: 18836476 DOI: 10.1038/onc.2008.274]

33 **Ma L**, Teruya-Feldstein J, Weinberg RA. Tumour invasion and metastasis initiated by microRNA-10b in breast cancer. *Nature* 2007; **449**: 682-688 [PMID: 17898713 DOI: 10.1038/nature06174]

34 **He L**, Thomson JM, Hemann MT, Hernando-Monge E, Mu D, Goodson S, Powers S, Cordon-Cardo C, Lowe SW, Hannon GJ, Hammond SM. A microRNA polycistron as a potential human oncogene. *Nature* 2005; **435**: 828-833 [PMID: 15944707 DOI: 10.1038/nature03552]

35 **Mraz M**, Pospisilova S, Malinova K, Slapak I, Mayer J. MicroRNAs in chronic lymphocytic leukemia pathogenesis and disease subtypes. *Leuk Lymphoma* 2009; **50**: 506-509 [PMID: 19347736 DOI: 10.1080/10428190902763517]

36 **Zabolotneva AA**, Zhavoronkov AA, Shegay PV, Gaifullin NM, Alekseev BY, Roumiantsev SA, Garazha AV, Kovalchuk O, Aravin A, Buzdin AA. A systematic experimental evaluation of microRNA markers of human bladder cancer. *Front Genet* 2013; **4**: 247 [PMID: 24298280 DOI: 10.3389/fgene.2013.00247]

37 **Sandhu R**, Rivenbark AG, Mackler RM, Livasy CA, Coleman WB. Dysregulation of microRNA expression drives aberrant DNA hypermethylation in basal-like breast cancer. *Int J Oncol* 2013; [Epub ahead of print] [PMID: 24297604 DOI: 10.3892/ijo.2013.2197]

38 **Roy R,** De Sarkar N, Ghose S, Paul RR, Pal M, Bhattacharya C, Chowdhury SK, Ghosh S, Roy B. Genetic variations at microRNA and processing genes and risk of oral cancer. *Tumour Biol* 2013; [Epub ahead of print] [PMID: 24297336 DOI: 10.1007/s13277-013-1450-3]

39 **Sun F**, Chen HG, Li W, Yang X, Wang X, Jiang R, Guo Z, Chen H, Huang J, Borowsky AD, Qiu Y. Androgen receptor splice variant AR3 promotes prostate cancer via modulating expression of autocrine/paracrine factors. *J Biol Chem* 2013; [Epub ahead of print] [PMID: 24297183 DOI: 10.1074/jbc.M113.492140]

40 **Yu H**, Gao G, Jiang L, Guo L, Lin M, Jiao X, Jia W, Huang J. Decreased expression of miR-218 is associated with poor prognosis in patients with colorectal cancer. *Int J Clin Exp Pathol* 2013; **6**: 2904-2911 [PMID: 24294377]

41 **Lee HY**, Mohammed KA, Kaye F, Sharma P, Moudgil BM, Clapp WL, Nasreen N. Targeted delivery of let-7a microRNA encapsulated ephrin-A1 conjugated liposomal nanoparticles inhibit tumor growth in lung cancer. *Int J Nanomedicine* 2013; **8**: 4481-4494 [PMID: 24293999 DOI: 10.2147/IJN.S41782]

42 **Pauley KM**, Cha S, Chan EK. MicroRNA in autoimmunity and autoimmune diseases. *J Autoimmun* 2009; **32**: 189-194 [PMID: 19303254 DOI: 10.1016/j.jaut.2009.02.012]

43 **Sonkoly E**, Pivarcsi A. Advances in microRNAs: implications for immunity and inflammatory diseases. *J Cell Mol Med* 2009; **13**: 24-38 [PMID: 19175698 DOI: 10.1111/j.1582-4934.2008.00534.x]

44 **Lodish HF**, Zhou B, Liu G, Chen CZ. Micromanagement of the immune system by microRNAs. *Nat Rev Immunol* 2008; **8**: 120-130 [PMID: 18204468 DOI: 10.1038/nri2252]

45 **Zhao Y**, Ransom JF, Li A, Vedantham V, von Drehle M, Muth AN, Tsuchihashi T, McManus MT, Schwartz RJ, Srivastava D. Dysregulation of cardiogenesis, cardiac conduction, and cell cycle in mice lacking miRNA-1-2. *Cell* 2007; **129**: 303-317 [PMID: 17397913 DOI: 10.1016/j.cell.2007.03.030]

46 **Thum T**, Galuppo P, Wolf C, Fiedler J, Kneitz S, van Laake LW, Doevendans PA, Mummery CL, Borlak J, Haverich A, Gross C, Engelhardt S, Ertl G, Bauersachs J. MicroRNAs in the human heart: a clue to fetal gene reprogramming in heart failure. *Circulation* 2007; **116**: 258-267 [PMID: 17606841 DOI: 10.1161/CIRCULATIONAHA.107.687947]

47 **Zhao Y**, Samal E, Srivastava D. Serum response factor regulates a muscle-specific microRNA that targets Hand2 during cardiogenesis. *Nature* 2005; **436**: 214-220 [PMID: 15951802 DOI: 10.1038/nature03817]

48 **Carè A**, Catalucci D, Felicetti F, Bonci D, Addario A, Gallo P, Bang ML, Segnalini P, Gu Y, Dalton ND, Elia L, Latronico MV, Høydal M, Autore C, Russo MA, Dorn GW, Ellingsen O, Ruiz-Lozano P, Peterson KL, Croce CM, Peschle C, Condorelli G. MicroRNA-133 controls cardiac hypertrophy. *Nat Med* 2007; **13**: 613-618 [PMID: 17468766 DOI: 10.1038/nm1582]

49 **Zhu H**, Shyh-Chang N, Segrè AV, Shinoda G, Shah SP, Einhorn WS, Takeuchi A, Engreitz JM, Hagan JP, Kharas MG, Urbach A, Thornton JE, Triboulet R, Gregory RI, Altshuler D, Daley GQ. The Lin28/let-7 axis regulates glucose metabolism. *Cell* 2011; **147**: 81-94 [PMID: 21962509 DOI: 10.1016/j.cell.2011.08.033]

50 **Frost RJ**, Olson EN. Control of glucose homeostasis and insulin sensitivity by the Let-7 family of microRNAs. *Proc Natl Acad Sci U S A* 2011; **108**: 21075-21080 [PMID: 22160727 DOI: 10.1073/pnas.1118922109]

51 **Maes OC**, Chertkow HM, Wang E, Schipper HM. MicroRNA: Implications for Alzheimer Disease and other Human CNS Disorders. *Curr Genomics* 2009; **10**: 154-168 [PMID: 19881909 DOI: 10.2174/138920209788185252]

52 **Wu F**, Zikusoka M, Trindade A, Dassopoulos T, Harris ML, Bayless TM, Brant SR, Chakravarti S, Kwon JH. MicroRNAs are differentially expressed in ulcerative colitis and alter expression of macrophage inflammatory peptide-2 alpha. *Gastroenterology* 2008; **135**: 1624-1635.e24 [PMID: 18835392 DOI: 10.1053/j.gastro.2008.07.068]

53 **Wu F**, Dassopoulos T, Cope L, Maitra A, Brant SR, Harris ML, Bayless TM, Parmigiani G, Chakravarti S. Genome-wide gene expression differences in Crohn's disease and ulcerative colitis from endoscopic pinch biopsies: insights into distinctive pathogenesis. *Inflamm Bowel Dis* 2007; **13**: 807-821 [PMID: 17262812 DOI: 10.1002/ibd.20110]

54 **Bian Z**, Li L, Cui J, Zhang H, Liu Y, Zhang CY, Zen K. Role of miR-150-targeting c-Myb in colonic epithelial disruption during dextran sulphate sodium-induced murine experimental colitis and human ulcerative colitis. *J Pathol* 2011; **225**: 544-553 [PMID: 21590770 DOI: 10.1002/path.2907]

55 **Xiao C**, Calado DP, Galler G, Thai TH, Patterson HC, Wang J, Rajewsky N, Bender TP, Rajewsky K. MiR-150 controls B cell differentiation by targeting the transcription factor c-Myb. *Cell* 2007; **131**: 146-159 [PMID: 17923094 DOI: 10.1016/j.cell.2007.07.021]

56 **Van Itallie CM**, Anderson JM. Claudins and epithelial paracellular transport. *Annu Rev Physiol* 2006; **68**: 403-429 [PMID: 16460278 DOI: 10.1146/annurev.physiol.68.040104.131404]

57 **Furuse M**, Tsukita S. Claudins in occluding junctions of humans and flies. *Trends Cell Biol* 2006; **16**: 181-188 [PMID: 16537104 DOI: 10.1016/j.tcb.2006.02.006]

58 **Angelow S**, Ahlstrom R, Yu AS. Biology of claudins. *Am J Physiol Renal Physiol* 2008; **295**: F867-F876 [PMID: 18480174 DOI: 10.1152/ajprenal.90264.2008]

59 **Ye D**, Guo S, Al-Sadi R, Ma TY. MicroRNA regulation of intestinal epithelial tight junction permeability. *Gastroenterology* 2011; **141**: 1323-1333 [PMID: 21763238 DOI: 10.1053/j.gastro.2011.07.005]

60 **Qin W**, Ren Q, Liu T, Huang Y, Wang J. MicroRNA-155 is a novel suppressor of ovarian cancer-initiating cells that targets CLDN1. *FEBS Lett* 2013; **587**: 1434-1439 [PMID: 23523916 DOI: 10.1016/j.febslet.2013.03.023]

61 **Li Q**, Zhu F, Chen P. miR-7 and miR-218 epigenetically control tumor suppressor genes RASSF1A and Claudin-6 by targeting HoxB3 in breast cancer. *Biochem Biophys Res Commun* 2012; **424**: 28-33 [PMID: 22705304 DOI: 10.1016/j.bbrc.2012.06.028]

62 **Mishra R**, Singh SK. HIV-1 Tat C modulates expression of miRNA-101 to suppress VE-cadherin in human brain microvascular endothelial cells. *J Neurosci* 2013; **33**: 5992-6000 [PMID: 23554480 DOI: 10.1523/JNEUROSCI.4796-12.2013]

63 **Furuse M**. Molecular basis of the core structure of tight junctions. *Cold Spring Harb Perspect Biol* 2010; **2**: a002907 [PMID: 20182608 DOI: 10.1101/cshperspect.a002907]

64 **Tang Y**, Banan A, Forsyth CB, Fields JZ, Lau CK, Zhang LJ, Keshavarzian A. Effect of alcohol on miR-212 expression in intestinal epithelial cells and its potential role in alcoholic liver disease. *Alcohol Clin Exp Res* 2008; **32**: 355-364 [PMID: 18162065 DOI: 10.1111/j.1530-0277.2007.00584.x]

65 **Lu LF**, Liston A. MicroRNA in the immune system, microRNA as an immune system. *Immunology* 2009; **127**: 291-298 [PMID: 19538248 DOI: 10.1111/j.1365-2567.2009.03092.x]

66 **Chen CZ**, Li L, Lodish HF, Bartel DP. MicroRNAs modulate hematopoietic lineage differentiation. *Science* 2004; **303**: 83-86 [PMID: 14657504 DOI: 10.1126/science.1091903]

67 **Zhou B**, Wang S, Mayr C, Bartel DP, Lodish HF. miR-150, a microRNA expressed in mature B and T cells, blocks early B cell development when expressed prematurely. *Proc Natl Acad Sci U S A* 2007; **104**: 7080-7085 [PMID: 17438277 DOI: 10.1073/pnas.0702409104]

68 **Dunne A**, O'Neill LA. Adaptor usage and Toll-like receptor signaling specificity. *FEBS Lett* 2005; **579**: 3330-3335 [PMID: 15876435 DOI: 10.1016/j.febslet.2005.04.024]

69 **Kracht M**, Saklatvala J. Transcriptional and post-transcriptional control of gene expression in inflammation. *Cytokine* 2002; **20**: 91-106 [PMID: 12453467]

70 **Taganov KD**, Boldin MP, Chang KJ, Baltimore D. NF-kappaB-dependent induction of microRNA miR-146, an inhibitor targeted to signaling proteins of innate immune responses. *Proc Natl Acad Sci U S A* 2006; **103**: 12481-12486 [PMID: 16885212 DOI: 10.1073/pnas.0605298103]

71 **Ceppi M**, Pereira PM, Dunand-Sauthier I, Barras E, Reith W, Santos MA, Pierre P. MicroRNA-155 modulates the interleukin-1 signaling pathway in activated human monocyte-derived dendritic cells. *Proc Natl Acad Sci U S A* 2009; **106**: 2735-2740 [PMID: 19193853 DOI: 10.1073/pnas.0811073106]

72 **O'Connell RM**, Taganov KD, Boldin MP, Cheng G, Baltimore D. MicroRNA-155 is induced during the macrophage inflammatory response. *Proc Natl Acad Sci U S A* 2007; **104**: 1604-1609 [PMID: 17242365 DOI: 10.1073/pnas.0610731104]

73 **Nakamachi Y**, Kawano S, Takenokuchi M, Nishimura K, Sakai Y, Chin T, Saura R, Kurosaka M, Kumagai S. MicroRNA-124a is a key regulator of proliferation and monocyte chemoattractant protein 1 secretion in fibroblast-like synoviocytes from patients with rheumatoid arthritis. *Arthritis Rheum* 2009; **60**: 1294-1304 [PMID: 19404929 DOI: 10.1002/art.24475]

74 **Nagata Y**, Nakasa T, Mochizuki Y, Ishikawa M, Miyaki S, Shibuya H, Yamasaki K, Adachi N, Asahara H, Ochi M. Induction of apoptosis in the synovium of mice with autoantibody-mediated arthritis by the intraarticular injection of double-stranded MicroRNA-15a. *Arthritis Rheum* 2009; **60**: 2677-2683 [PMID: 19714650 DOI: 10.1002/art.24762]

75 **Otaegui D**, Baranzini SE, Armañanzas R, Calvo B, Muñoz-Culla M, Khankhanian P, Inza I, Lozano JA, Castillo-Triviño T, Asensio A, Olaskoaga J, López de Munain A. Differential micro RNA expression in PBMC from multiple sclerosis patients. *PLoS One* 2009; **4**: e6309 [PMID: 19617918 DOI: 10.1371/journal.pone.0006309]

76 **Padgett KA**, Lan RY, Leung PC, Lleo A, Dawson K, Pfeiff J, Mao TK, Coppel RL, Ansari AA, Gershwin ME. Primary biliary cirrhosis is associated with altered hepatic microRNA expression. *J Autoimmun* 2009; **32**: 246-253 [PMID: 19345069 DOI: 10.1016/j.jaut.2009.02.022]

77 **Dai Y**, Huang YS, Tang M, Lv TY, Hu CX, Tan YH, Xu ZM, Yin YB. Microarray analysis of microRNA expression in peripheral blood cells of systemic lupus erythematosus patients. *Lupus* 2007; **16**: 939-946 [PMID: 18042587 DOI: 10.1177/0961203307084158]

78 **Sonkoly E**, Wei T, Janson PC, Sääf A, Lundeberg L, Tengvall-Linder M, Norstedt G, Alenius H, Homey B, Scheynius A, Ståhle M, Pivarcsi A. MicroRNAs: novel regulators involved in the pathogenesis of psoriasis? *PLoS One* 2007; **2**: e610 [PMID: 17622355 DOI: 10.1371/journal.pone.0000610]

79 **Godwin JG**, Ge X, Stephan K, Jurisch A, Tullius SG, Iacomini J. Identification of a microRNA signature of renal ischemia reperfusion injury. *Proc Natl Acad Sci U S A* 2010; **107**: 14339-14344 [PMID: 20651252 DOI: 10.1073/pnas.0912701107]

80 **Ren J**, Pulakat L, Whaley-Connell A, Sowers JR. Mitochondrial biogenesis in the metabolic syndrome and cardiovascular disease. *J Mol Med* (Berl) 2010; **88**: 993-1001 [PMID: 20725711 DOI: 10.1007/s00109-010-0663-9]

81 **Kim JA**, Wei Y, Sowers JR. Role of mitochondrial dysfunction in insulin resistance. *Circ Res* 2008; **102**: 401-414 [PMID: 18309108 DOI: 10.1161/CIRCRESAHA.107.165472]

82 **West AP**, Shadel GS, Ghosh S. Mitochondria in innate immune responses. *Nat Rev Immunol* 2011; **11**: 389-402 [PMID: 21597473 DOI: 10.1038/nri2975]

83 **Makino A**, Scott BT, Dillmann WH. Mitochondrial fragmentation and superoxide anion production in coronary endothelial cells from a mouse model of type 1 diabetes. *Diabetologia* 2010; **53**: 1783-1794 [PMID: 20461356 DOI: 10.1007/s00125-010-1770-4]

84 **Aschrafi A**, Schwechter AD, Mameza MG, Natera-Naranjo O, Gioio AE, Kaplan BB. MicroRNA-338 regulates local cytochrome c oxidase IV mRNA levels and oxidative phosphorylation in the axons of sympathetic neurons. *J Neurosci* 2008; **28**: 12581-12590 [PMID: 19020050 DOI: 10.1523/JNEUROSCI.3338-08.2008]

85 **Oba S**, Kumano S, Suzuki E, Nishimatsu H, Takahashi M, Takamori H, Kasuya M, Ogawa Y, Sato K, Kimura K, Homma Y, Hirata Y, Fujita T. miR-200b precursor can ameliorate renal tubulointerstitial fibrosis. *PLoS One* 2010; **5**: e13614 [PMID: 21049046 DOI: 10.1371/journal.pone.0013614]

86 **Nishi H**, Ono K, Iwanaga Y, Horie T, Nagao K, Takemura G, Kinoshita M, Kuwabara Y, Mori RT, Hasegawa K, Kita T, Kimura T. MicroRNA-15b modulates cellular ATP levels and degenerates mitochondria via Arl2 in neonatal rat cardiac myocytes. *J Biol Chem* 2010; **285**: 4920-4930 [PMID: 20007690 DOI: 10.1074/jbc.M109.082610]

87 **Gao P**, Tchernyshyov I, Chang TC, Lee YS, Kita K, Ochi T, Zeller KI, De Marzo AM, Van Eyk JE, Mendell JT, Dang CV. c-Myc suppression of miR-23a/b enhances mitochondrial glutaminase expression and glutamine metabolism. *Nature* 2009; **458**: 762-765 [PMID: 19219026 DOI: 10.1038/nature07823]

88 **Yuan C**, Chen WX, Zhu JS, Chen NW, Lu YM, Ou YX, Chen HQ. IL-10 treatment is associated with prohibitin expression in the Crohn's disease intestinal fibrosis mouse model. *Mediators Inflamm* 2013; **2013**: 617145 [PMID: 23690666 DOI: 10.1155/2013/617145]

89 **He C,** Klionsky DJ. Regulation mechanisms and signaling pathways of autophagy. *Annu Rev Genet* 2009; **43**: 67-93 [PMID: 19653858 DOI: 10.1146/annurev-genet-102808-114910]

90 **Mizushima N**, Yoshimori T, Levine B. Methods in mammalian autophagy research. *Cell* 2010; **140**: 313-326 [PMID: 20144757 DOI: 10.1016/j.cell.2010.01.028]

91 **Lapaquette P**, Glasser AL, Huett A, Xavier RJ, Darfeuille-Michaud A. Crohn's disease-associated adherent-invasive E. coli are selectively favoured by impaired autophagy to replicate intracellularly. *Cell Microbiol* 2010; **12**: 99-113 [PMID: 19747213 DOI: 10.1111/j.1462-5822.2009.01381.x]

92 **Kuballa P**, Huett A, Rioux JD, Daly MJ, Xavier RJ. Impaired autophagy of an intracellular pathogen induced by a Crohn's disease associated ATG16L1 variant. *PLoS One* 2008; **3**: e3391 [PMID: 18852889 DOI: 10.1371/journal.pone.0003391]

93 **Mizushima N**, Yoshimori T, Ohsumi Y. The role of Atg proteins in autophagosome formation. *Annu Rev Cell Dev Biol* 2011; **27**: 107-132 [PMID: 21801009 DOI: 10.1146/annurev-cellbio-092910-154005]

94 **Noda T**, Yoshimori T. Molecular basis of canonical and bactericidal autophagy. *Int Immunol* 2009; **21**: 1199-1204 [PMID: 19737785 DOI: 10.1093/intimm/dxp088]

95 **Lu C,** Chen J, Xu HG, Zhou X, He Q, Li YL, Jiang G, Shan Y, Xue B, Zhao RX, Wang Y, Werle KD, Cui R, Liang J, Xu ZX. MIR106B and MIR93 Prevent Removal of Bacteria From Epithelial Cells by Disrupting ATG16L1-Mediated Autophagy. *Gastroenterology* 2013; [Epub ahead of print] [PMID: 24036151 DOI: 10.1053/j.gastro.2013.09.006]

96 **Ghorpade DS**, Sinha AY, Holla S, Singh V, Balaji KN. NOD2-Nitric Oxide-responsive MicroRNA-146a Activates Sonic Hedgehog Signaling to Orchestrate Inflammatory Responses in Murine Model of Inflammatory Bowel Disease. *J Biol Chem* 2013; **288**: 33037-33048 [PMID: 24092752 DOI: 10.1074/jbc.M113.492496]

97 **Brest P**, Lapaquette P, Souidi M, Lebrigand K, Cesaro A, Vouret-Craviari V, Mari B, Barbry P, Mosnier JF, Hébuterne X, Harel-Bellan A, Mograbi B, Darfeuille-Michaud A, Hofman P. A synonymous variant in IRGM alters a binding site for miR-196 and causes deregulation of IRGM-dependent xenophagy in Crohn's disease. *Nat Genet* 2011; **43**: 242-245 [PMID: 21278745 DOI: 10.1038/ng.762]

98 **Esquela-Kerscher A**, Slack FJ. Oncomirs - microRNAs with a role in cancer. *Nat Rev Cancer* 2006; **6**: 259-269 [PMID: 16557279 DOI: 10.1038/nrc1840]

99 **Fasseu M**, Tréton X, Guichard C, Pedruzzi E, Cazals-Hatem D, Richard C, Aparicio T, Daniel F, Soulé JC, Moreau R, Bouhnik Y, Laburthe M, Groyer A, Ogier-Denis E. Identification of restricted subsets of mature microRNA abnormally expressed in inactive colonic mucosa of patients with inflammatory bowel disease. *PLoS One* 2010; **5**: [PMID: 20957151 DOI: 10.1371/journal.pone.0013160]

100 **Zahm AM**, Thayu M, Hand NJ, Horner A, Leonard MB, Friedman JR. Circulating microRNA is a biomarker of pediatric Crohn disease. *J Pediatr Gastroenterol Nutr* 2011; **53**: 26-33 [PMID: 21546856 DOI: 10.1097/MPG.0b013e31822200cc]

101 **Zhou R**, Hu G, Gong AY, Chen XM. Binding of NF-kappaB p65 subunit to the promoter elements is involved in LPS-induced transactivation of miRNA genes in human biliary epithelial cells. *Nucleic Acids Res* 2010; **38**: 3222-3232 [PMID: 20144951 DOI: 10.1093/nar/gkq056]

102 **Iborra M**, Bernuzzi F, Correale C, Vetrano S, Fiorino G, Beltrán B, Marabita F, Locati M, Spinelli A, Nos P, Invernizzi P, Danese S. Identification of serum and tissue micro-RNA expression profiles in different stages of inflammatory bowel disease. *Clin Exp Immunol* 2013; **173**: 250-258 [PMID: 23607522 DOI: 10.1111/cei.12104]

103 **Janssen HL**, Reesink HW, Lawitz EJ, Zeuzem S, Rodriguez-Torres M, Patel K, van der Meer AJ, Patick AK, Chen A, Zhou Y, Persson R, King BD, Kauppinen S, Levin AA, Hodges MR. Treatment of HCV infection by targeting microRNA. *N Engl J Med* 2013; **368**: 1685-1694 [PMID: 23534542 DOI: 10.1056/NEJMoa1209026]

104 **Misso G**, Zappavigna S, Castellano M, De Rosa G, Di Martino MT, Tagliaferri P, Tassone P, Caraglia M. Emerging pathways as individualized therapeutic target of multiple myeloma. *Expert Opin Biol Ther* 2013; **13** Suppl 1: S95-109 [PMID: 23738692 DOI: 10.1517/14712598.2013.807338]

105 **Rossi M**, Pitari MR, Amodio N, Di Martino MT, Conforti F, Leone E, Botta C, Paolino FM, Del Giudice T, Iuliano E, Caraglia M, Ferrarini M, Giordano A, Tagliaferri P, Tassone P. miR-29b negatively regulates human osteoclastic cell differentiation and function: implications for the treatment of multiple myeloma-related bone disease. *J Cell Physiol* 2013; **228**: 1506-1515 [PMID: 23254643 DOI: 10.1002/jcp.24306]

106 **Amodio N**, Leotta M, Bellizzi D, Di Martino MT, D'Aquila P, Lionetti M, Fabiani F, Leone E, Gullà AM, Passarino G, Caraglia M, Negrini M, Neri A, Giordano A, Tagliaferri P, Tassone P. DNA-demethylating and anti-tumor activity of synthetic miR-29b mimics in multiple myeloma. *Oncotarget* 2012; **3**: 1246-1258 [PMID: 23100393]

107 **Amodio N**, Di Martino MT, Foresta U, Leone E, Lionetti M, Leotta M, Gullà AM, Pitari MR, Conforti F, Rossi M, Agosti V, Fulciniti M, Misso G, Morabito F, Ferrarini M, Neri A, Caraglia M, Munshi NC, Anderson KC, Tagliaferri P, Tassone P. miR-29b sensitizes multiple myeloma cells to bortezomib-induced apoptosis through the activation of a feedback loop with the transcription factor Sp1. *Cell Death Dis* 2012; **3**: e436 [PMID: 23190608 DOI: 10.1038/cddis.2012.175]

 **P-Reviewers:** Caraglia M, de Magistris L **S-Editor:** Qi Y

**L-Editor: E-Editor:**

**Figure 1 Summary of the role of microRNAs in inflammatory bowel disease.** IBD: Inflammatory bowel disease.

**Y**

**Nucleus**

**Mitochondria**

**Autophagesome**

**TLR**

**IRAK1**

**MyoD88**

**TRAF**

**NF-κB**

**Inflammation**

**NOD2**

**SHH**

**Cyotochrom C**

**IBD**

**Tight junction proteins**

**miRNAs**